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Extension

PULSAR Extension: Clinical Improvements Maintained Over 156 Weeks With Aflibercept 8 mg in Patients With Neovascular Age-Related Macular Degeneration

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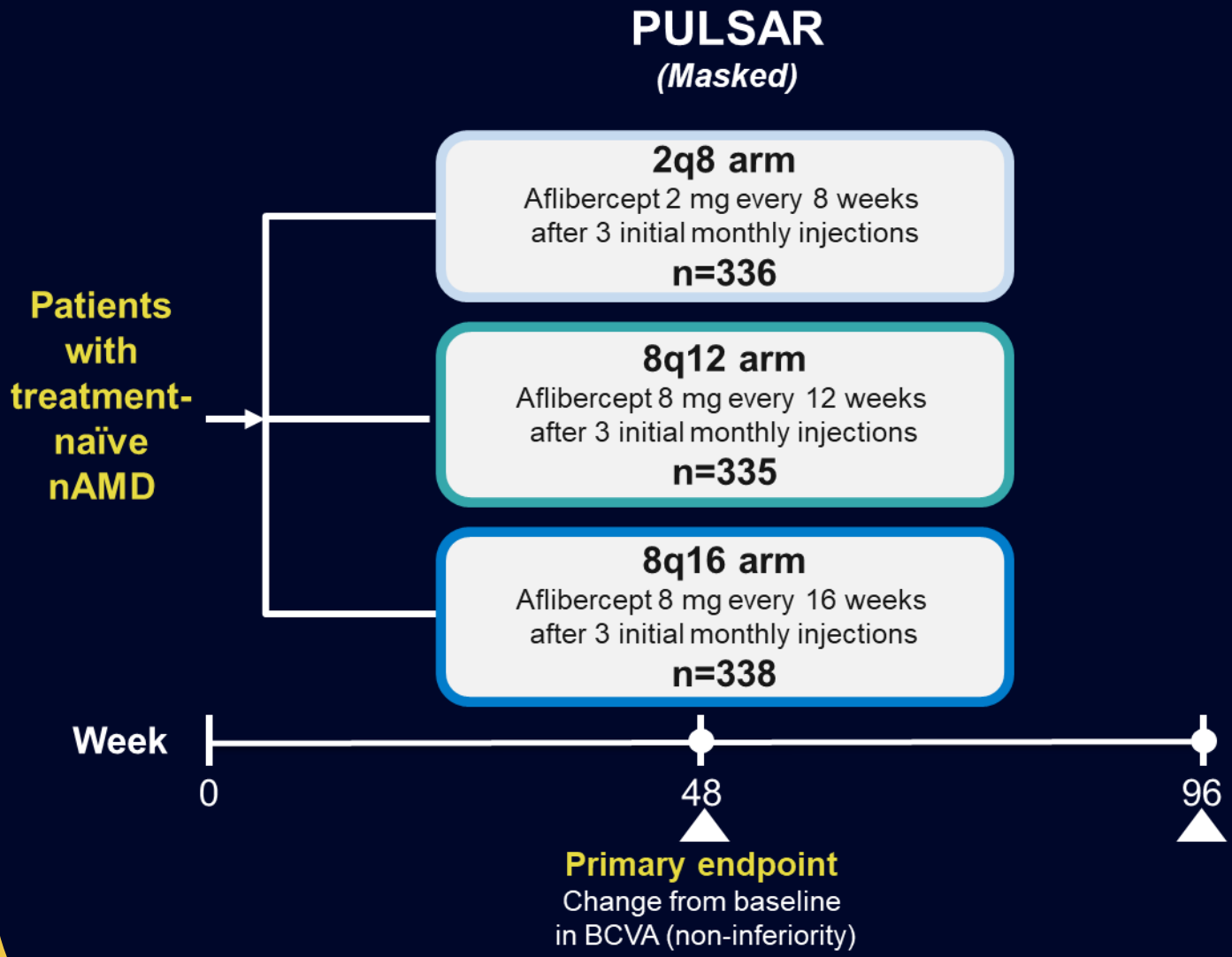
PULSAR Extension Design



[a]To be eligible for the Extension phase, patients had to have ≥1 BCVA and CRT assessments between Week 84 and Week 92.
BCVA, best-corrected visual acuity; **CRT**, central subfield retinal thickness; **nAMD**, neovascular age-related macular degeneration.

PULSAR Weeks 48 and 96: Key Results

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Articles

Intravitreal aflibercept 8 mg in neovascular age-related macular degeneration (PULSAR): 48-week results from a randomised, double-masked, non-inferiority, phase 3 trial

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Summary

Background Intravitreal aflibercept 8 mg could improve treatment outcomes and provide sustained disease control in patients with neovascular age-related macular degeneration (nAMD), with extended dosing compared with aflibercept 2 mg.

Methods PULSAR is a phase 3, randomised, three-group, double-masked, non-inferiority, 96-week trial conducted across 223 sites worldwide. Adults with nAMD were randomised 1:1:1 to aflibercept 8 mg every 12 weeks (8q12), aflibercept 8 mg every 16 weeks (8q16), or aflibercept 2 mg every 8 weeks (2q8), following three initial monthly doses in all groups. From week 16, patients in the aflibercept 8 mg groups had their dosing interval shortened if pre-specified dose regimen modification criteria denoting disease activity were met. The primary endpoint was change from baseline in best-corrected visual acuity (BCVA) at week 48. All patients with at least one dose of study treatment were included in the efficacy and safety analyses. This trial is registered with ClinicalTrials.gov (NCT04423718) and is ongoing.

Findings Of 1011 patients randomised to aflibercept 8q12 (n=336), 8q16 (n=338), or 2q8 (n=337) between Aug 11, 2020, and July 30, 2021, 1009 patients received study treatment (aflibercept 8q12 n=335; aflibercept 8q16 n=338; and aflibercept 2q8 n=336). Aflibercept 8q12 and 8q16 showed non-inferior BCVA gains versus aflibercept 2q8 (mean BCVA change from baseline +6·7 [SD 12·6] and +6·2 [11·7] *vs* +7·6 [12·2] letters). The least squares mean differences between aflibercept 8q12 versus 2q8 and 8q16 versus 2q8, respectively, were −0·97 (95% CI −2·87 to 0·92) and −1·14 (−2·97 to 0·69) letters (non-inferiority margin at 4 letters). The incidence of ocular adverse events in the study eye was similar across groups (aflibercept 8q12 n=129 [39%]; aflibercept 8q16 n=127 [38%]; and aflibercept 2q8 n=130 [39%]).

Interpretation Aflibercept 8 mg showed efficacy and safety with extended dosing intervals, which has the potential to improve the management of patients with nAMD.

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Introduction

Age-related macular degeneration (AMD) is a major cause of visual impairment worldwide that is expected to increase in prevalence as populations age.[1] It has been projected to affect 288 million individuals by 2040.[1] Before the advent of treatments targeting vascular endothelial growth factor (VEGF), the neovascular form of AMD (nAMD) was responsible for up to 90% of cases of severe vision loss (20/200 or worse) secondary to AMD.[2]

Pathological alteration in VEGF signalling plays a central role in the development of nAMD by stimulating choroidal angiogenesis, increasing vascular permeability, and ultimately resulting in fluid accumulation in the retina.[3,4] As fluid accumulation can be associated with visual impairment,[5] adequate fluid resolution in the macula is an important outcome of treatment options in nAMD.

Intravitreal anti-VEGF therapies provided improvements in visual and anatomic outcomes in clinical trials.[6–8] However, the high treatment burden associated with frequent clinic visits and injections represents a considerable challenge in the routine management of patients with nAMD,[9,10] which can result in inconsistent dosing regimens and consequent losses of initial treatment benefits.

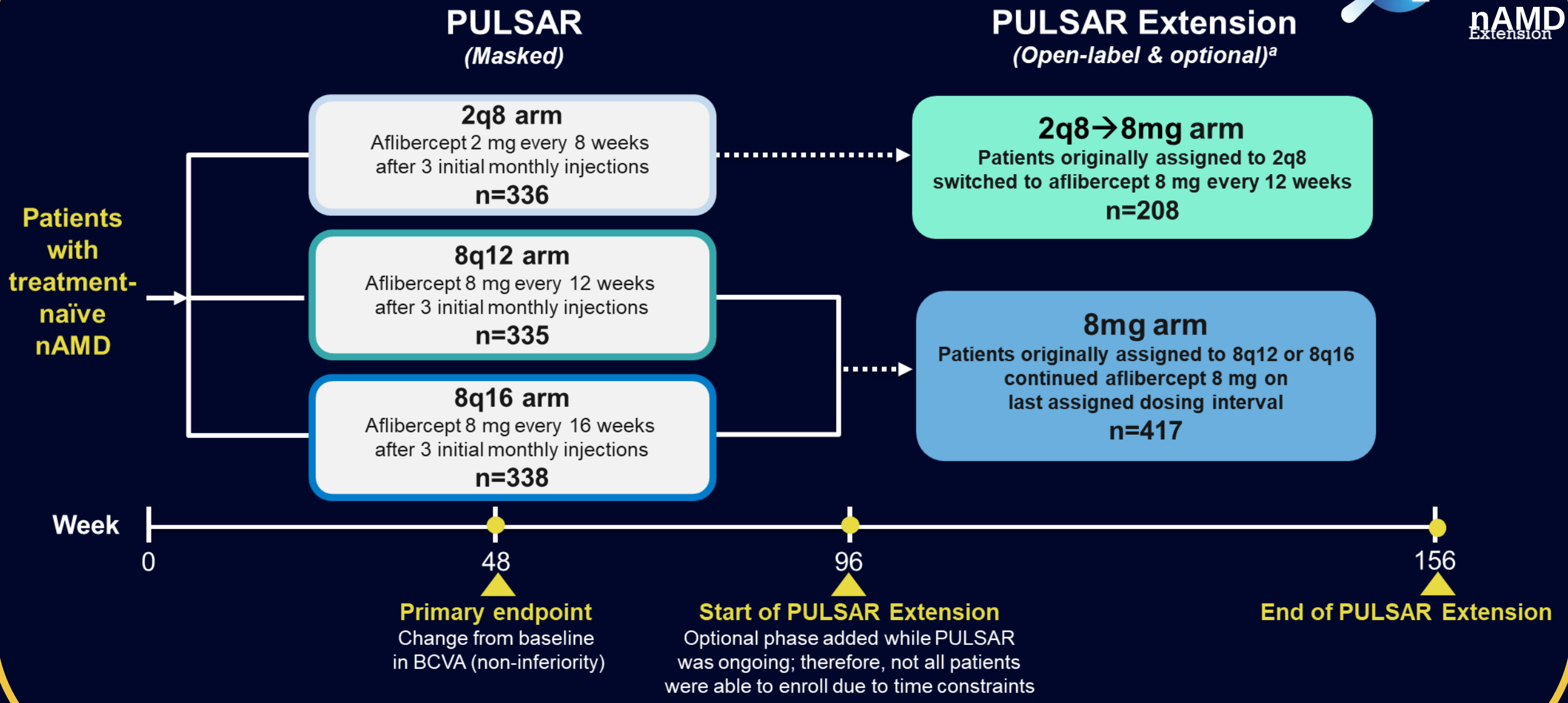
Previous studies explored the use of different doses of anti-VEGF agents and the corresponding visual and anatomical response, with varying outcomes.[11–18] The SAVE trial suggested benefits with ranibizumab 2 mg in patients with recalcitrant nAMD,[12,19] and the HARBOR trial suggested increased durability with ranibizumab 2 mg versus 0·5 mg, but without improved visual and anatomic outcomes associated with the higher dose.[16] The CLEAR-IT 2 trial showed greater reduction in central

At Weeks 48 and 96, patients receiving aflibercept 8 mg achieved comparable visual and anatomic outcomes to those receiving aflibercept 2 mg but with fewer injections

At Weeks 48 and 96, most patients in the aflibercept 8 mg group attained extended dosing intervals of ≥12 weeks

At Weeks 48 and 96, the safety profile of aflibercept 8 mg was comparable to that of aflibercept 2 mg, and no new safety concerns were identified

PULSAR Extension Design



[a]To be eligible for the Extension phase, patients had to have ≥1 BCVA and CRT assessments between Week 84 and Week 92.
BCVA, best-corrected visual acuity; **CRT**, central subfield retinal thickness; **nAMD**, neovascular age-related macular degeneration.

PULSAR Extension Design

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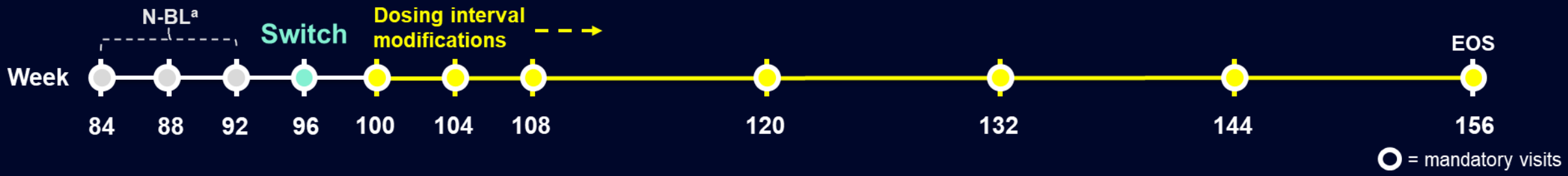
2q8→8mg
n=208

Patients initially treated with aflibercept 2q8 were switched to aflibercept 8 mg at Week 96 and immediately assigned to a 12-week dosing interval

8mg
n=417

Patients initially treated with aflibercept 8q12 or 8q16 continued with aflibercept 8 mg at their last assigned dosing interval



E-DRM: Interval Shortening During Year 3

- Patients were assessed at ***any visit*** beginning at Week 100
- **Criteria for interval shortening:**
  - >5-letter loss in BCVA from N-BL due to persistent or worsening nAMD **AND** either:
    - >25 µm increase in CRT from N-BL **OR**
    - New onset of foveal neovascularization **OR**
    - New foveal hemorrhage
  - **OR** >10-letter loss in BCVA from N-BL due to worsening nAMD
- Dosing intervals shortened by **2-week** increments to a **minimum of Q8**

E-DRM: Interval Extension During Year 3

- Patients were assessed at ***dosing visits*** beginning at Week 100
- **Criteria for interval extension:**
  - <5-letter loss in BCVA from N-BL **AND**
  - No fluid (IRF or SRF) in the central subfield on OCT **AND**
  - No new onset foveal neovascularization or foveal hemorrhage
- Dosing intervals extended by **2-week** increments to a **maximum of Q24**

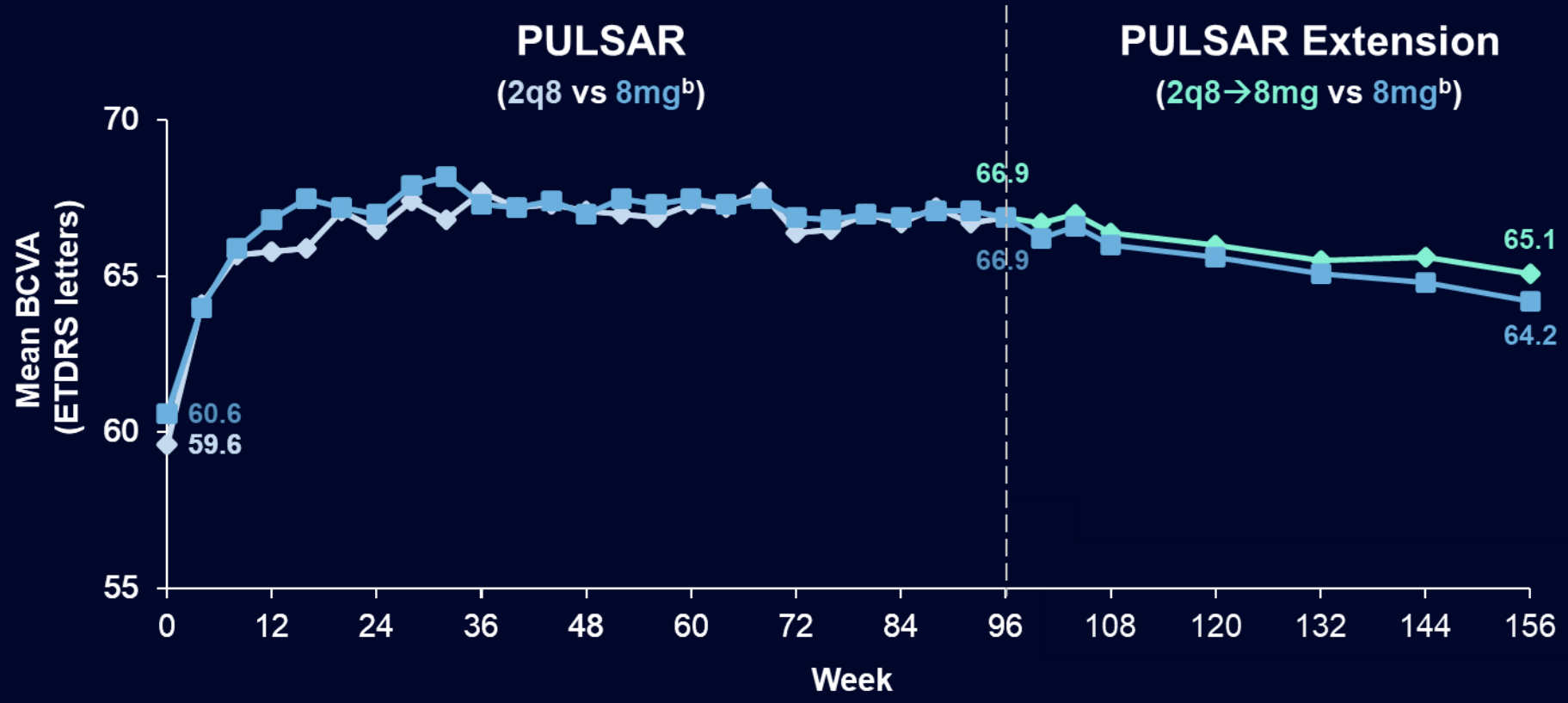
[a]N-BL was an average of values from Weeks 84, 88, and 92. **E-DRM**, dosing regimen modification criteria during the PULSAR Extension; **EOS**, end of study; **IRF**, intraretinal fluid; **SRF**, subretinal fluid; **N-BL**, new baseline; **OCT**, optical coherence tomography; **Q8**, every 8 weeks; **Q24**, every 24 weeks.

Patient Disposition & Baseline Characteristics

	PULSAR	PULSAR Extension		
	Total	2q8→8mg	8mg	Total
Patients entering PULSAR study (FAS), n	1009	–	–	–
Patients entering PULSAR Extension (eFAS), n (%)	–	208 (61.9)[a]	417 (62.0)[a]	625 (61.9)[a]
Completion rate at Week 96, %	85.9	–	–	–
Completion rate at Week 156, %	–	89.9[b]	90.4[b]	90.2[b]
Age (years)	74 (8.4)	73.9 (8.2)	74.0 (8.1)	74.0 (8.1)
Female, %	54.5	58.7	55.2	56.3
Race, %				
White	75.8	77.4	77.5	77.4
Black or African American	0.4	0.5	0.5	0.5
Asian	23.2	22.1	21.1	21.4
Other[c]	0.6	0	1.0	0.6
History of hypertension, %	64.3	63.0	65.0	64.3
BCVA (ETDRS letters)	59.6 (13.3)	59.6 (13.7)	60.6 (12.7)	60.3 (13.0)
CRT (μm)[d]	369 (130)	365 (139)	375 (132)	371 (134)
Total lesion area, mm^2	6.7 (5.4)	6.8 (5.0)	6.4 (5.2)	6.6 (5.1)
Lesion type, %				
Occult	58.2	57.7	57.1	57.5
Predominantly classic	20.7	23.1	22.4	18.8
Minimally classic	18.6	15.9	18.1	20.3

Data are mean±SD unless otherwise stated; data are for patients in the FAS (PULSAR) and eFAS (PULSAR Extension) at the main study baseline. [a]Proportions were calculated based on the number of patients who initially entered the main PULSAR study. [b]Completion rate for PULSAR Extension based on eFAS. [c]Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races, and unreported race. [d]Data as assessed by reading center. **eFAS**, PULSAR Extension FAS; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **FAS**, full analysis set, **SD**, standard deviation.

Mean BCVA[a] Through Week 156



Mean number of injections from baseline to Week 96[c]

2q8: 12.8

8q12/8q16: 8.9

Mean number of injections from Week 96 to Week 156[c]

2q8→8mg: 4.7

8mg: 3.8

Note: At Week 156, the 2q8→8mg group (n=208) and 8mg group (n=417) reported a LS mean change (MMRM) from baseline in BCVA of +4.6 and +3.4 letters, respectively. [a]eFAS (observed cases). [b]Patients who were randomly assigned to the 8q12 or 8q16 groups at the beginning of the PULSAR study and continued treatment with aflibercept 8 mg through the PULSAR Extension. [c]eSAF.
eSAF, safety analysis set in the PULSAR Extension; **LS**, least squares; **MMRM,** mixed model for repeated measures, used to generate least square means for the eFAS with baseline BCVA as a covariate; treatment group (aflibercept 8q12, 8q16, 2q8), visit, and stratification variables (geographic region [Japan vs rest of the world] and baseline BCVA [<60 vs ≥60 letters]) as fixed factors; and terms for the interaction between visit and baseline BCVA and the interaction between visit and treatment.

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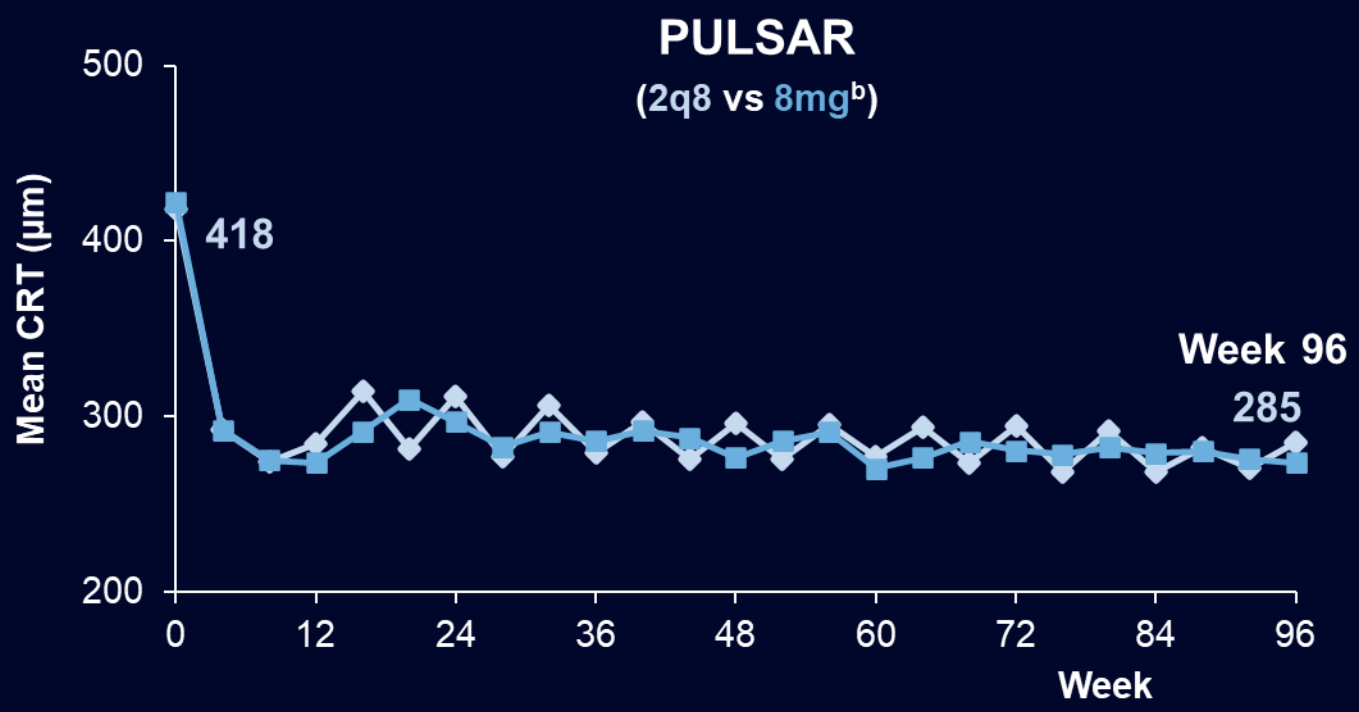
Mean CRT[a] Through Week 156



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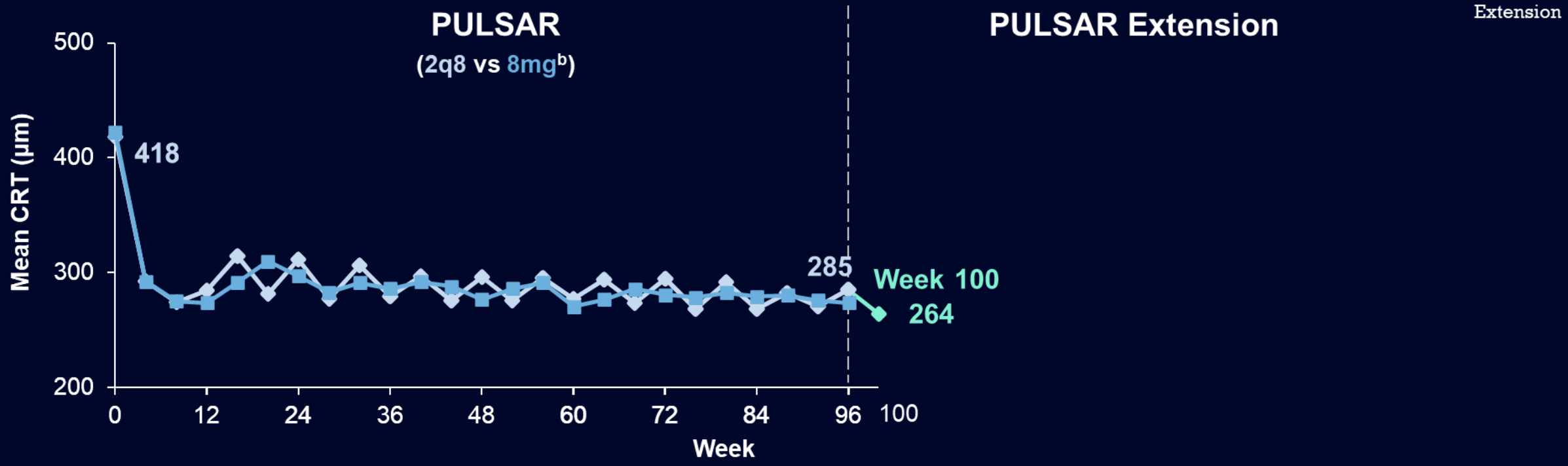
Mean CRT[a] Through Week 156



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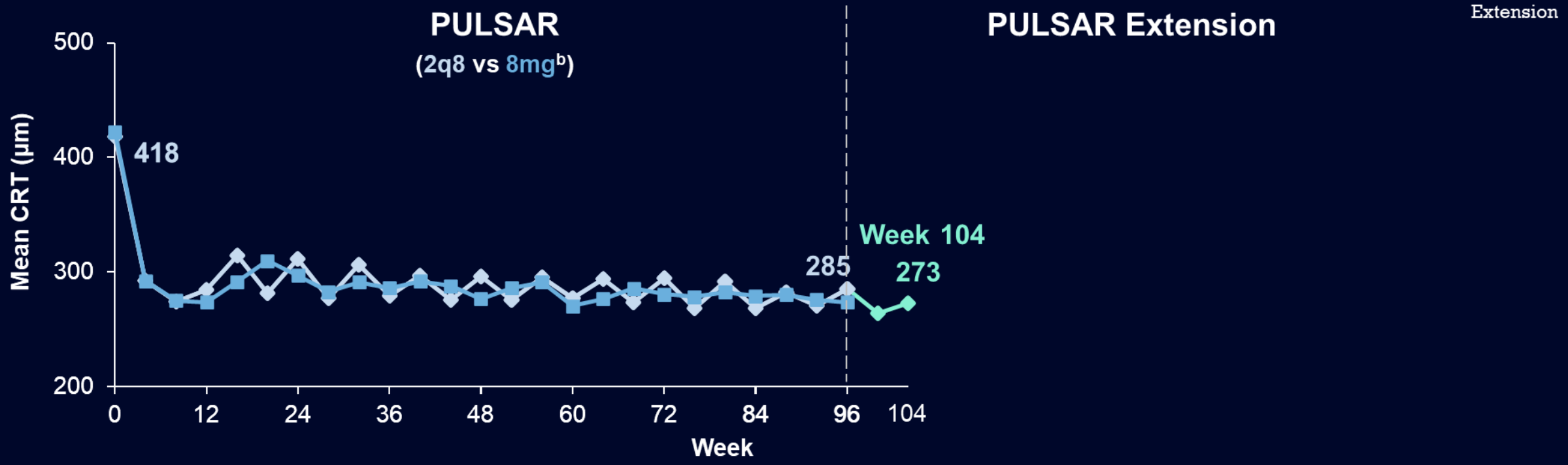
nAMD

Mean CRT[a] Through Week 156



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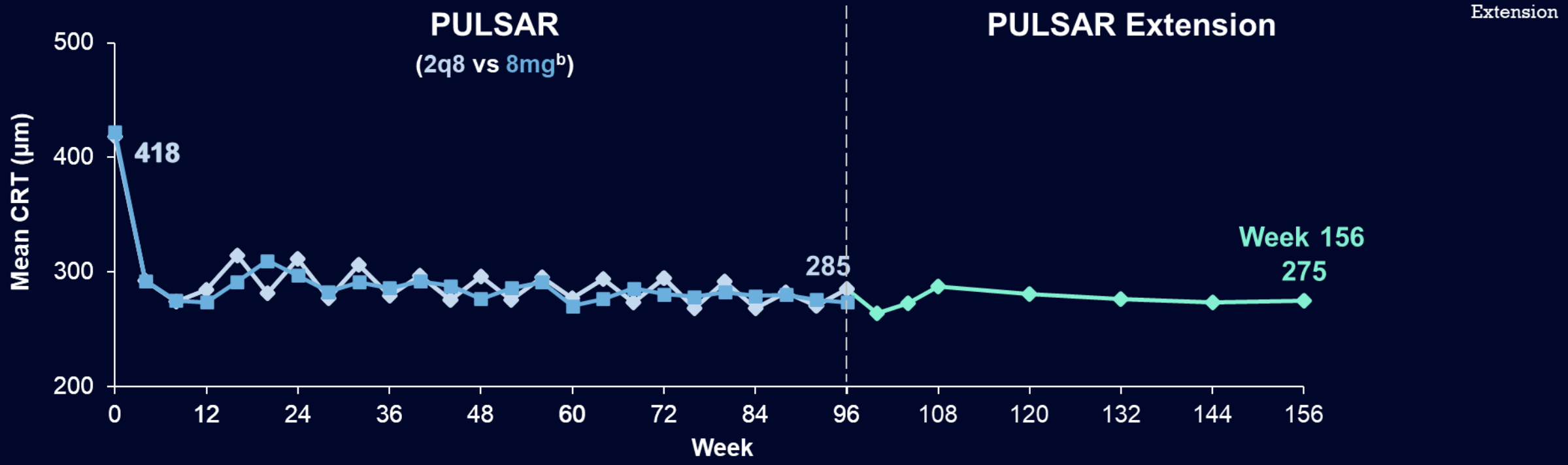
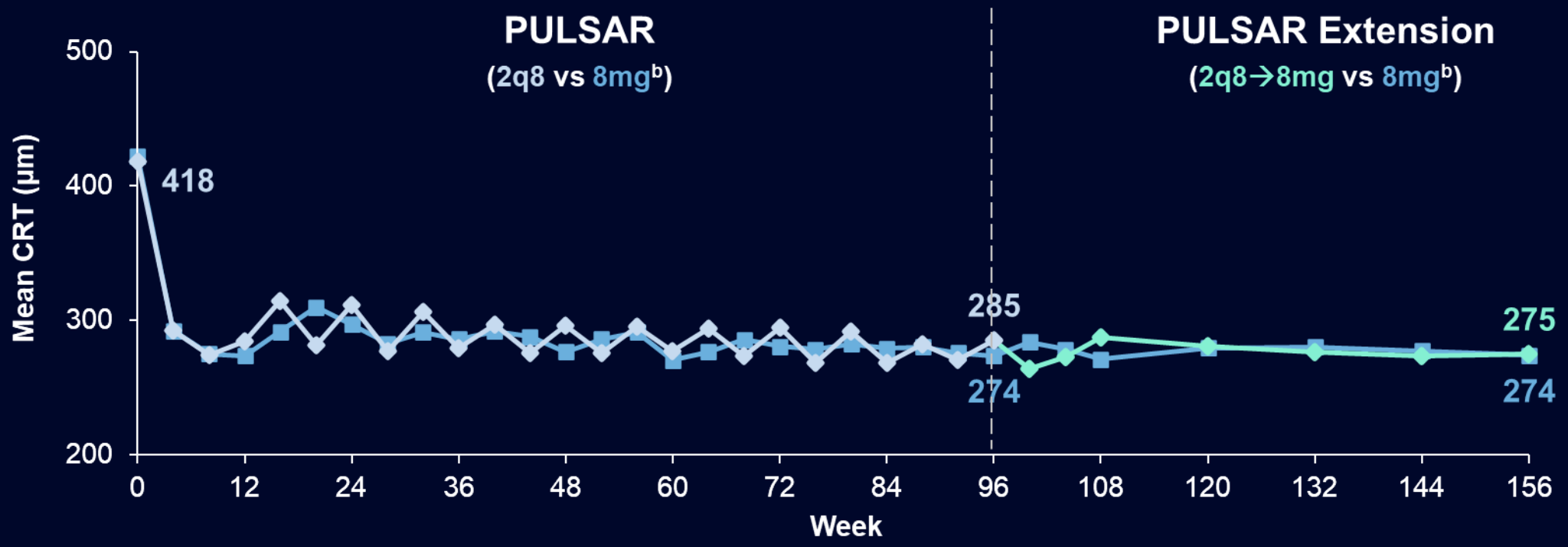
Mean CRT[a] Through Week 156



Mean CRT[a] Through Week 156



Note: At Week 156, the 2q8→8mg group (n=208) and 8mg group (n=417) reported a LS mean change (MMRM)[c] from baseline in CRT of −145 µm and −148 µm, respectively. [a]eFAS (observed cases). [b]Patients who were randomly assigned to the 8q12 or 8q16 groups at the beginning of the PULSAR study and continued treatment with aflibercept 8 mg through the PULSAR Extension. [c]LS means were generated for the eFAS using MMRM with baseline CRT as a covariate; treatment group (aflibercept 8q12, 8q16, 2q8), visit, and stratification variables (geographic region [Japan vs rest of the world] and baseline BCVA [<60 vs ≥60 letters]) as fixed factors; and terms for the interaction between visit and baseline CRT and the interaction between visit and treatment.
CI, confidence intervals.

Majority of Aflibercept 8 mg-Treated Patients Completed Extended Dosing Intervals at Week 156

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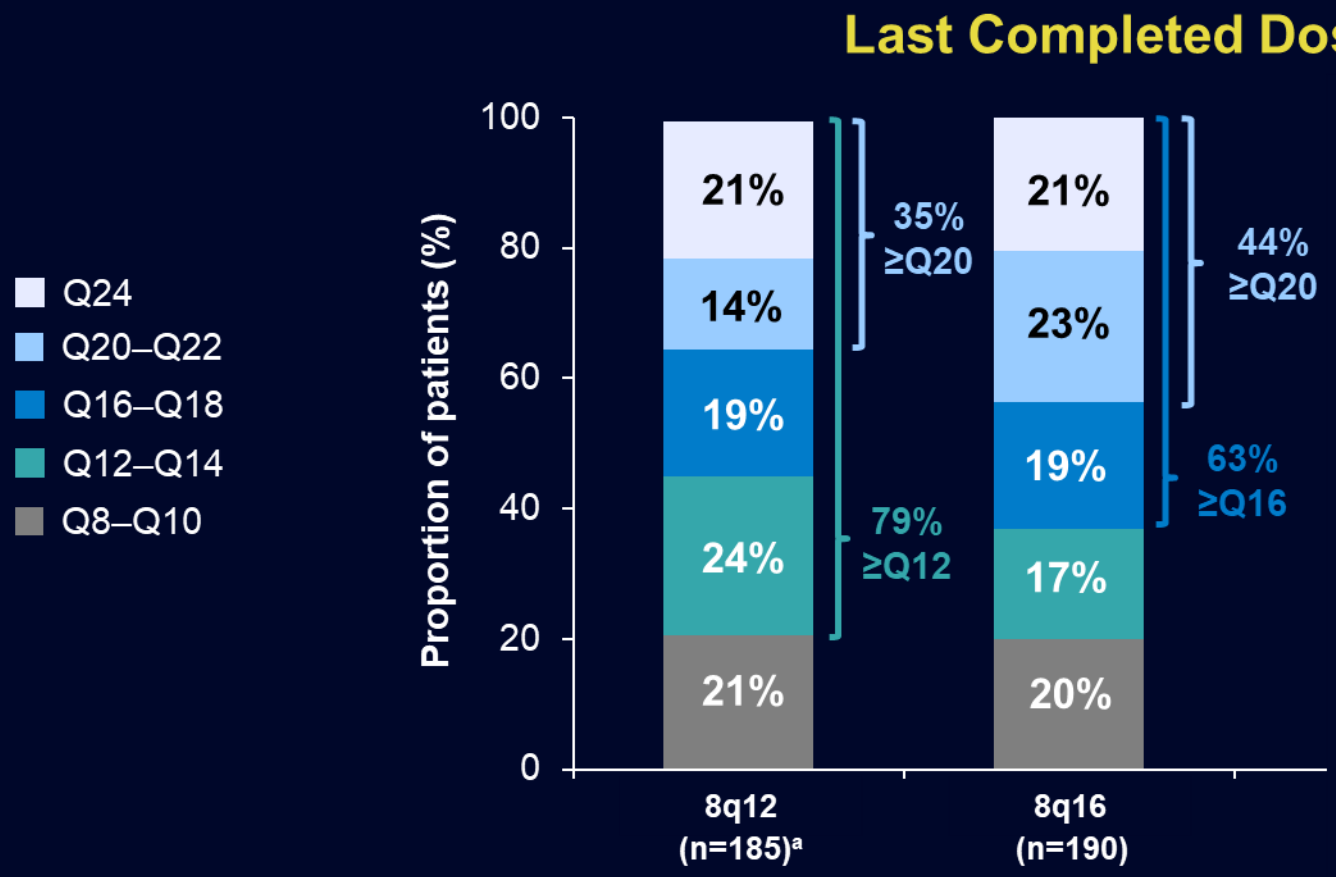
nAMD
Extension



eSAF, patients completing Week 156. Values may not add up to 100% due to rounding. [a]One patient had a missing value for this assessment. [b]Per protocol, patients in the 2q8→8mg group did not have sufficient time to complete a ≥Q20 dosing interval by Week 156; patients misassigned to longer dosing intervals are included here for completeness.

Majority of Aflibercept 8 mg-Treated Patients Completed Extended Dosing Intervals at Week 156

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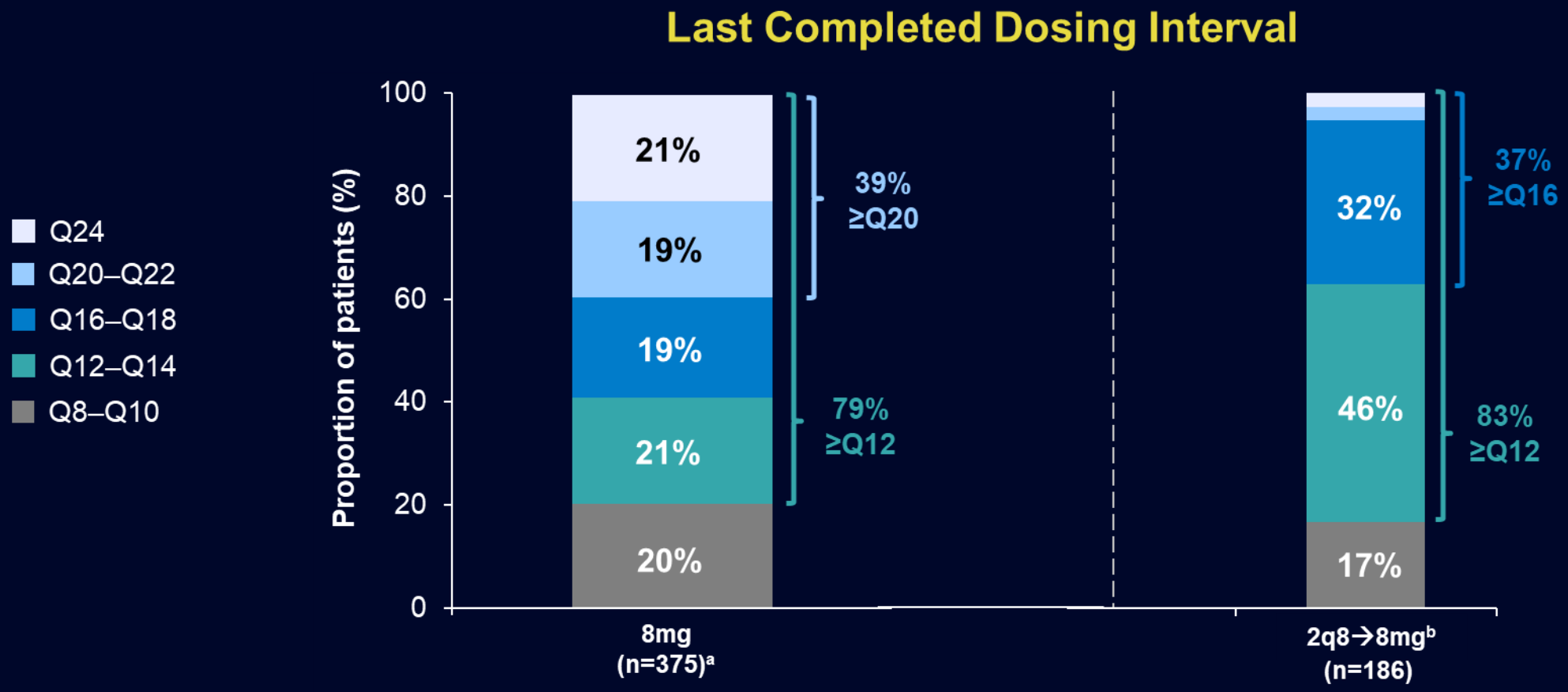
nAMD
Extension



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Majority of Aflibercept 8 mg-Treated Patients Assigned Extended Dosing Intervals at Week 156

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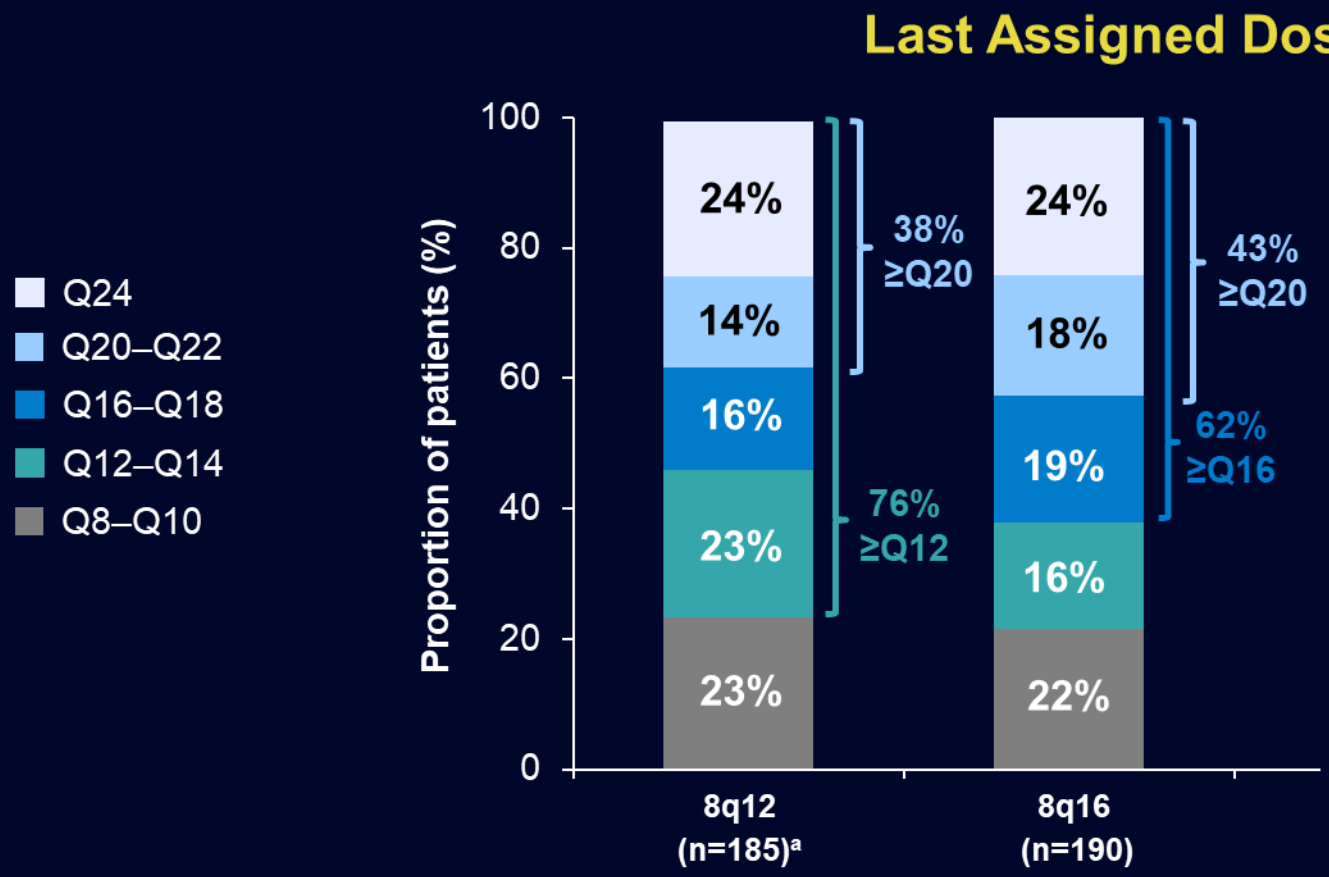
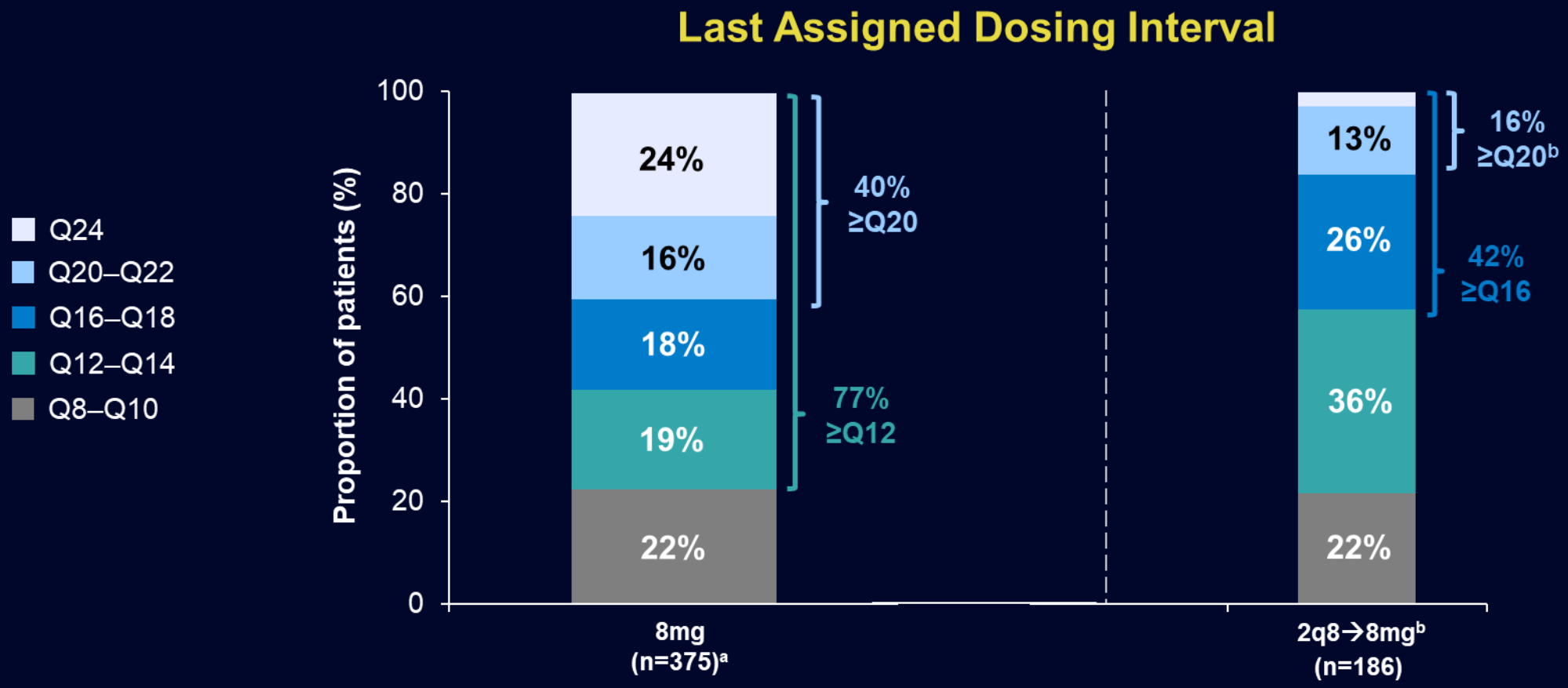
Extension



eSAF, patients completing Week 156. Values may not add up to 100% due to rounding. [a]One patient had a missing value for this assessment. [b]Per protocol, patients in the 2q8→8mg group did not have sufficient time to achieve a last assigned dosing interval of >Q20 by Week 156; patients misassigned to longer dosing intervals are included for completeness.

Majority of Aflibercept 8 mg-Treated Patients Assigned Extended Dosing Intervals at Week 156

pulsar nAMD Extension



eSAF, patients completing Week 156. Values may not add up to 100% due to rounding. [a]One patient had a missing value for this assessment. [b]Per protocol, patients in the 2q8→8mg group did not have sufficient time to achieve a last assigned dosing interval of >Q20 by Week 156; patients misassigned to longer dosing intervals are included for completeness.

Reduction in CNV Lesion Area Through Week 156

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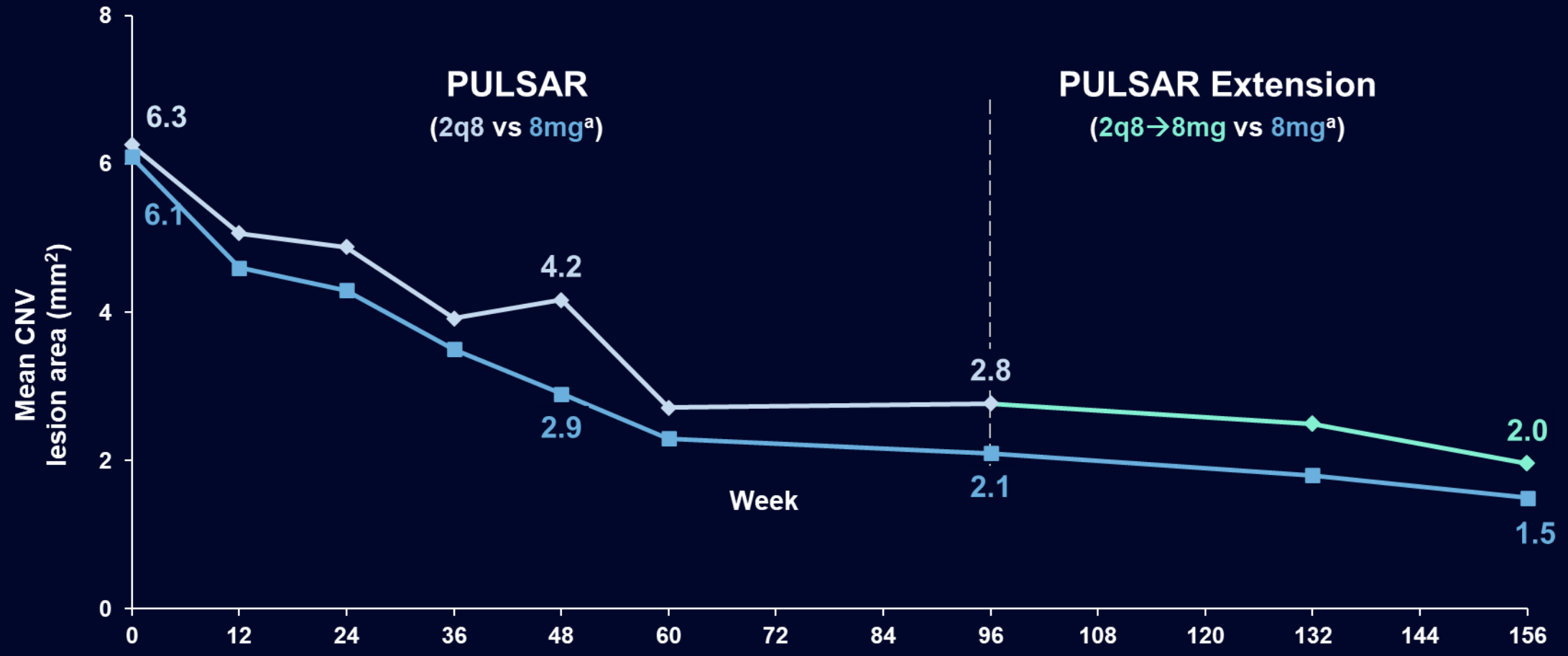
Extension



eFAS (observed cases). [a]Patients who were randomly assigned to the 8q12 or 8q16 groups at the beginning of the PULSAR study and continued treatment with aflibercept 8 mg through the PULSAR Extension. [b]LS means were generated for the eFAS using MMRM with baseline CNV as a covariate; treatment group (aflibercept 8q12, 8q16, 2q8), visit, and stratification variables (geographic region [Japan vs rest of the world] and baseline BCVA [<60 vs ≥60 letters]) as fixed factors; and terms for the interaction between visit and baseline CNV and the interaction between visit and treatment.

Fewer Patients With Macular Leakage on FA Through Week 156

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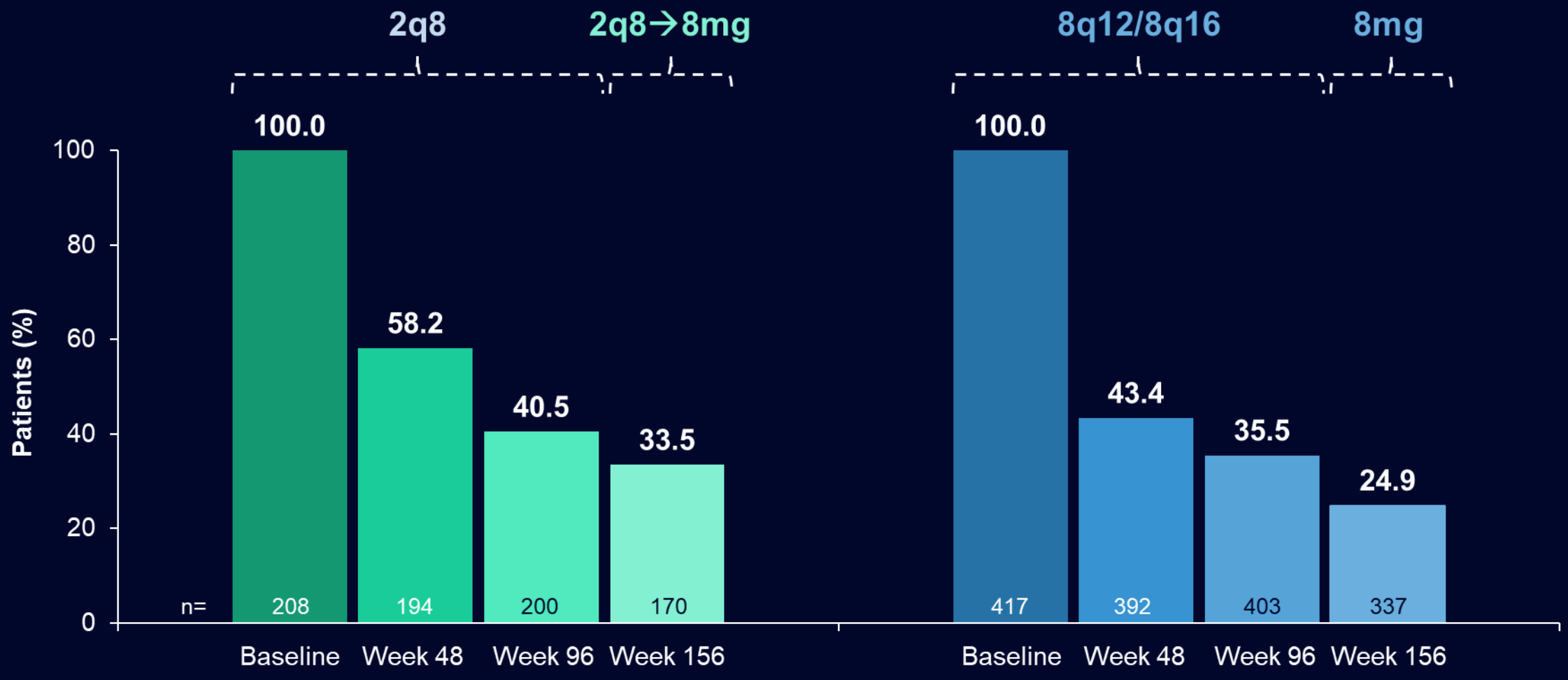

eFAS (OC); proportions at each timepoint calculated based on the n values indicated. FA, fluorescein angiography.

Ocular Safety From Main Baseline Through Week 156[a]

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	2q8→8mg	8mg	Total
N (eSAF)	208	417	625
Ocular TEAEs, n (%)	130 (62.5)	251 (60.2)	381 (61.0)
Ocular SAEs, n (%)	7(3.4)	21 (5.0)	28 (4.5)
Intraocular inflammation, n (%)	5 (2.4)	8 (1.9)	13 (2.1)
Eye inflammation	1 (0.5)	0	1 (0.2)
Iridocyclitis	1 (0.5)	3 (0.7)	4 (0.6)
Iritis	0	1 (0.2)	1 (0.2)
Uveitis	1 (0.5)	0	1 (0.2)
Vitreal cells	1 (0.5)	2 (0.5)	3 (0.5)
Vitritis	0	1 (0.2)	1 (0.2)
Chorioretinitis	0	1 (0.2)	1 (0.2)
Endophthalmitis	1 (0.5)	0	1 (0.2)

- Ocular TEAEs reported in ≥4% of all patients included cataract, retinal hemorrhage, visual acuity reduced, vitreous floaters, and intraocular pressure increased
- No cases of occlusive vasculitis were reported

[a]Cumulative events in the study eye from the main PULSAR study baseline through Week 156.
SAE, serious adverse event; **TEAE**, treatment-emergent adverse event.

Non-Ocular Safety From Main Baseline Through Week 156[a]

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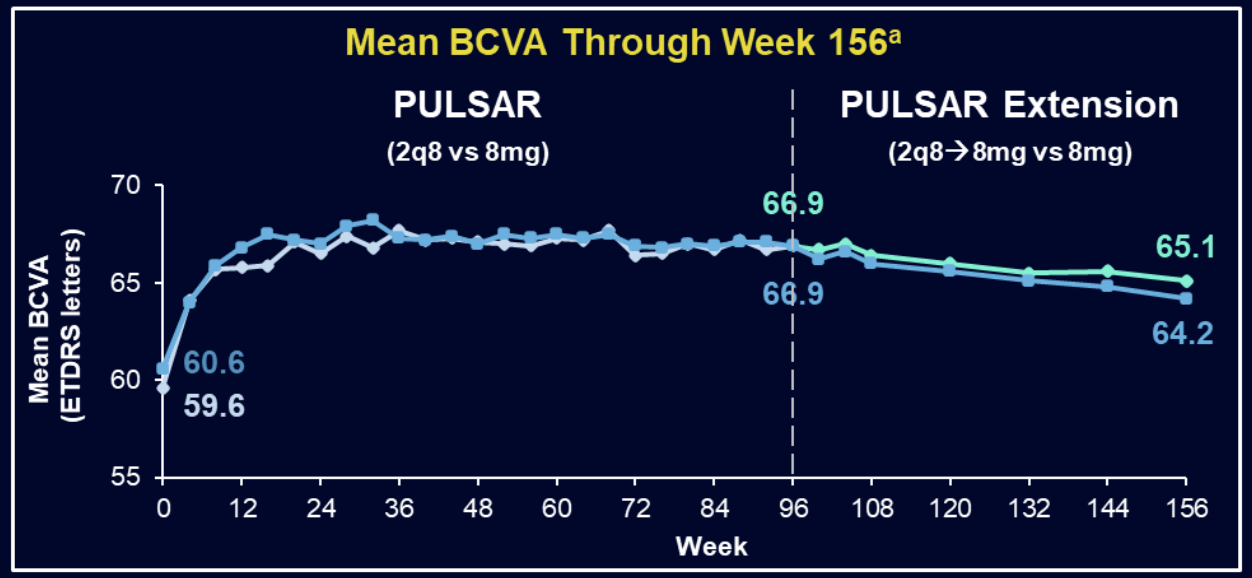
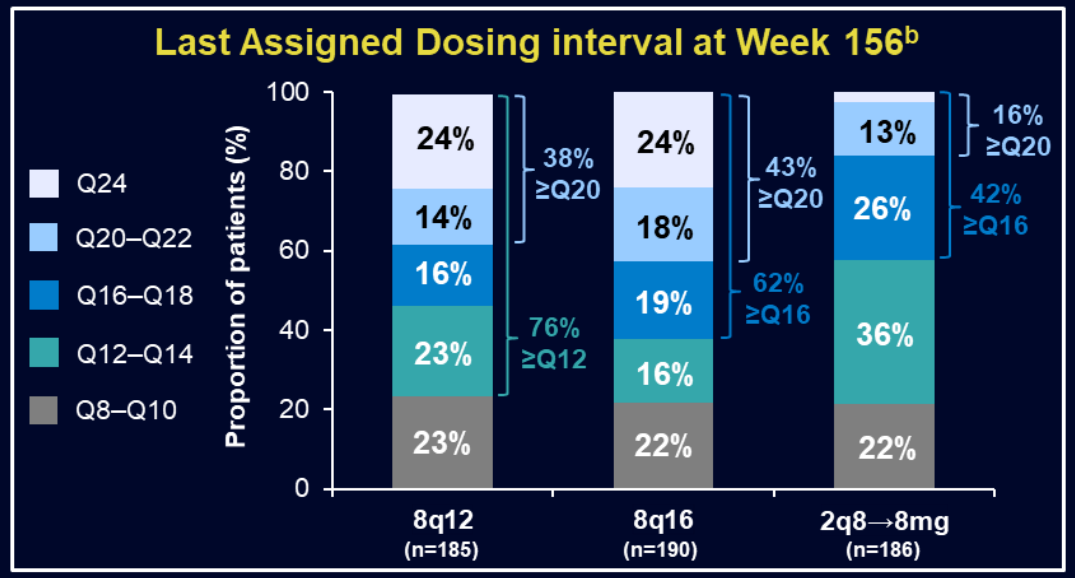
	2q8→8mg	8mg	Total
N (eSAF)	208	417	625
Non-ocular SAEs, n (%)	43 (20.7)	106 (25.4)	149 (23.8)
APTC events, n (%)	4 (1.9)	7 (1.7)	11 (1.8)
Deaths, n (%)	4 (1.9)	9 (2.2)	13 (2.1)

[a]Cumulative events in the study eye from the main PULSAR study baseline through Week 156.
APTC, Anti-Platelet Trialists' Collaboration.

PULSAR Extension: Key Week 156 Results

- In the PULSAR Extension, functional and anatomic improvements were sustained through Week 156 in the **2q8→8mg and 8mg groups**
- Mean BCVA and CRT were comparable at Week 156 between the **2q8→8mg and 8mg groups**
  - Patients in the **2q8→8mg group** achieved these improvements with **extended dosing intervals** and a **mean of 4.7 injections** from Week 96 through Week 156
- The majority of patients achieved extended dosing intervals at Week 156
- These findings suggest that patients with treatment-naïve nAMD can achieve **durable improvements with aflibercept 8 mg** administered over extended dosing intervals
- The safety profile of aflibercept 8 mg was comparable to that of aflibercept 2 mg





[a]eFAS, observed cases. [b]eSAF, patients completing Week 156.

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Thank you!

- The PULSAR study (NCT04423718) was sponsored by Bayer AG (Leverkusen, Germany) and co-funded by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA). The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of this presentation
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